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Physiology of Human Photosensitivity

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Summary: Human epileptic photosensitivity has been studied in several ways, with (a) visual stimulation that resembles the stimulation normally responsible for seizures, such as that from televisions or videogames, both of which typically use cathode ray tubes in which the display is created in a flickering pattern. Such stimulation is often rendered yet more epileptogenic by programmes with content that also involves flashing or patterned material; (b) elementary visual stimuli that enable inferences to be drawn concerning the physiological trigger mechanisms. The typographic distribution of epileptiform EEG activity in response to such stimuli has complemented this approach, leading to the inference that the trigger is cortical and requires sychronised mass action of neurons; and (c) stimuli that avoid paroxysmal EEG activity and permit an investigation of the subepileptic response to visual stimuli, using the evoked potential. This has revealed abnormalities in the cortical mechanisms that control the response to strong visual stimulation. **Key Words:** Physiology—Photosensitivity—Epilepsy—Photoparoxysmal response—Visual evoked potentials—Contrast gain control.

Photosensitive epilepsy has an overall incidence of 1.5/100,000 per year, which increases between the ages of 7 and 19 years, to seven per 100,000 per year (1). About 80% of subjects aged 7–19 years spend ≥1 h/day playing videogames (1). In recent years, the progressive increase in the number of seizures precipitated by videogames and by television (TV) (1–7) prompted a number of researchers to deepen the study of the physiology of human visual sensitivity. The different approaches can be summarized as follows.

a. Some researchers (6,8–12) have tried to define the physical characteristics of visual stimuli involved in precipitating seizures. This approach has been pursued by using complex visual stimuli similar to those appearing in commercially available products.
b. The probability of paroxysmal EEG activity has been studied in response to elementary visual stimuli, the spatial, temporal, and chromatic parameters of which can be manipulated (e.g., 13). The study of the topographic distribution of paroxysmal activity has complemented this approach.
c. Other investigators (14,15) have used transient and steady-state visual evoked potentials (VEPs) to characterize the subepileptic cortical response in individuals who show visual sensitivity to simple and structured visual stimuli.

Several inferences derive from these studies, which are useful for understanding the nature of the triggering mechanisms and the physiologic abnormalities of cortical excitability in visually sensitive patients.

Visual stimulation with commercially available videogames or cartoons has helped in identifying factors that are important in triggering seizures, and these can be categorized as hardware dependent or software dependent.

HARDWARE-DEPENDENT TRIGGERING MECHANISMS

Scan frequency of TV screen

Scan frequency is the speed with which the image appears on the screen, measured in frames per second. If scan frequency is <75 Hz, the image appears tremulous, with an effect defined as "flickering," caused by the monitor "repainting" its on-screen image at a speed that is slow enough to be detected by the human eye. When the scan frequency is sufficiently high, no flicker is visible, as happens on the monitors of personal computers, where the scan frequency usually exceeds 75 Hz. The standard TV screens have a scan frequency of 50 Hz (Europe), with a raster of 625 horizontal lines, or 60 Hz (United States), with a raster of 525 horizontal lines. The whole picture is transmitted 25 or 30 times per second,

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respectively, but the lines are scanned in an interlaced pattern, a set of odd-numbered lines being drawn, followed by a set of even-numbered lines, and so on repeatedly. Each set of odd/even lines is known as a field (50 or 60 per second, respectively). Two fields make up a frame (25 or 30 per second, respectively). If we label the field of odd lines O and the field of even lines E, the fields come in the order $O_1E_1O_2E_2$, etc. The point of doing this is to reduce flicker, without increasing bandwidth.

The 100-z TVs show 312.5 lines per field, just as 50-Hz screens do, but draw two fields of odd-numbered lines before drawing two fields of even-numbered lines and then repeating this cycle. In this case, the fields come in the order $O_1O_1E_1E_1O_2O_2E_2E_2$, etc., so that scan frequency is doubled, and flickering is much reduced. A number of studies have shown a higher safety of TV screens with scan frequency of 100 Hz compared with lower frequencies (9,16,17). The increased safety presumably reflects of the reduction of the 50-Hz component visible at distances from which the lines of the raster cannot be resolved.

SOFTWARE-DEPENDENT TRIGGERING MECHANISMS

Colored images in motion

Geometric patterns with specific characteristics of luminance, contrast, and color can be effective in triggering paroxysmal EEG responses or epileptic seizures (9,16,17). In 1997, in Japan, 685 children and adolescents experienced epileptic seizures while watching the same sequence of a popular cartoon broadcast on TV. The incriminated sequence included bright red/blue frames, alternated at 12.5 Hz (10,19). The red frames were formed by a phosphor having two peaks of wavelength, usually close to at 625 and 704 nm, with a luminance (as broadcast) of 45 cd/m^2, whereas the blue frames had a single broader peak at 452 nm, with a luminance of 70 cd/m^2 (10). Subsequently, various researchers have used chromatic stimuli combined in various geometric patterns or spread as diffuse light and have shown their effectiveness in triggering paroxysmal EEG responses (11,19).

The potential of chromatic stimuli to trigger seizures, particularly red light, had already been hypothesized in previous studies (8,20). In particular, Takahashi and co-workers (8,11,12) administered intermittent photic stimuli with wavelength-specific optical filters to visually sensitive patients with different epilepsy syndromes. These authors hypothesized two different pathophysiologic mechanisms: a "wavelength-dependent" mechanism and a "quantity-of-light–dependent" mechanism. In the first case, a photoparoxysmal response would be elicited when flashing light, with low luminance, is composed by red light with a wavelength >700 nm, primarily stimulating red cones. This mechanism would underlie visual sensitivity in both focal and generalized idiopathic epilepsies. For the second triggering mechanism, the only important factor would be the amount of light (luminance) required to elicit the photoparoxysmal response, irrespective of the wavelength of the stimulus. The quantity-of-light–dependent mechanism would underlie photosensitivity in severe myoclonic epilepsy (11).

The study of visual stimuli present in commercials (videogames or cartoons) led to the development of guidelines preventing exposure to epileptogenic material. These guidelines were based on studies of the elementary physical characteristics (21).

PHYSICAL CHARACTERISTICS AND PHYSIOLOGIC MECHANISMS UNDERLYING SEIZURE PRECIPITATION

The discovery that the majority of patients sensitive to flicker also are sensitive to patterns of various kinds has allowed a variety of inferences concerning the trigger mechanism, based on the studies of responses of single units in the visual system of animals. These inferences have been considered in detail in a number of publications and reviewed elsewhere, together with the evidence on which they are based (13).

The seizure trigger involves cortical cells

A paroxysmal EEG response occurs in the majority of patients with a history of photosensitive seizures when they are exposed to the intermittent collimated light from a xenon gas discharge lamp. In ~30% of patients, bright, large, continuously illuminated patterns of high-contrast stripes evoke a similar, although usually less pronounced, response. The response is probabilistic and depends on the spatial and temporal properties of the visual stimuli that evoke it. For example, the probability of a response increases with the length of stripes in the patterns shown in Fig. 1a–d. The effect of the length of line contour is consistent with a cortical locus for the trigger and suggests that the trigger involves cells with linear receptive fields. Some pattern-sensitive patients respond to only a limited range of pattern orientations. In those patients who have no astigmatism sufficient to blur one orientation preferentially, the orientation selectivity cannot be explained by peripheral factors and is indicative of a trigger involving neurons with oriented receptive fields, again consistent with a cortical trigger. Further evidence for a cortical trigger comes from the presentation of patterns with different orientation, such as those in Fig. 1d and e, presented simultaneously but separately to the two eyes. The probability of a paroxysmal response is less likely than that when both eyes see patterns with the same orientation, implicating neurons with binocular fields, which have a cortical locus.

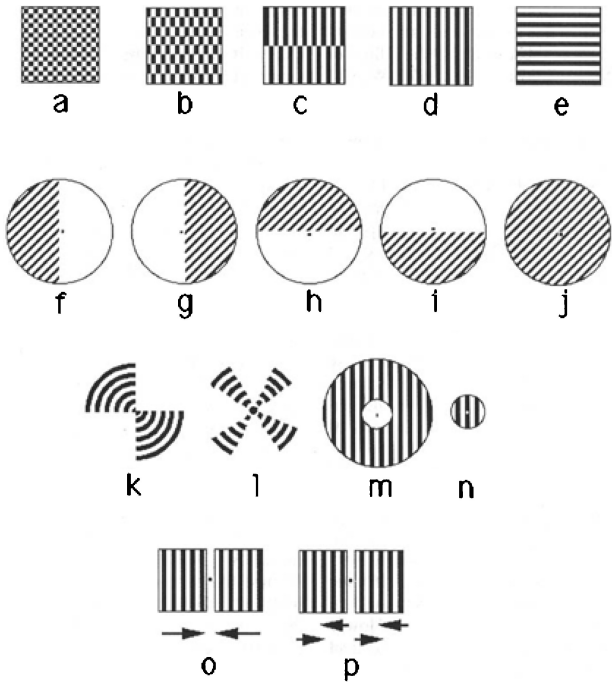

FIG. 1. Schematic diagrams of various patterns used in investigations of pattern-sensitive epilepsy. Most were printed on card and held against a tangent screen having the same space-averaged luminance as that of the patterns (~300 cd/m^2). The screen was lit with steady diffuse light and viewed, usually binocularly, from 0.6 m. The stripes had a square-wave luminance profile, spatial frequency usually 2 cycles/degree, and Michelson contrast of 0.7. They were increased in overall size until epileptiform EEG abnormalities were just detectable. For most patterns, the size was increased by increasing the outer radius, but for patterns of type m, the inner radius also was decreased on occasions. For patterns type k and l, the size of the angular sector was increased. The outer radius of the patterns varied from 2 to 28 degrees. The stripes in patterns of type o drifted in the direction of the arrows at velocities ≤14 degrees/s. The stripes the patterns of type p abruptly reversed their direction of motion after drifting at constant velocity the width of either one stripe or two. During each phase, the velocity was constant and comparable with that of the stripes in patterns of type o.

The probability of a paroxysmal response to patterns is maximal when the pattern has a spatial frequency of ~3 cycles/degree (i.e., when each pair of stripes in the pattern subtends ~20 min of arc at the eye)

The spatial-frequency selectivity remains the same whether the pattern is stationary or is vibrated to and fro in a direction orthogonal to the stripes through a distance of one stripe width or two. The vibratory motion of the pattern greatly increases the probability of a response, particularly when the frequency of the repetitive motion is ~20 Hz. Pattern motion on the retina also is generated by eye movements during steady gaze. The maximal response occurs when the spatial frequency of the pattern is ~3 cycles/degree, regardless of whether the amplitude of the motion is one stripe width or two. This suggests that the trigger involves neurons whose spatial tuning is independent of position in the visual field, and the first point at which this independence occurs is at the level of the complex cell in the visual cortex.

Two further lines of evidence for a cortical trigger come from the scalp topography of the EEG response itself

The response to patterns positioned in the upper or in the lower visual fields (Fig. 1h and i) can show a difference in vertical scalp distribution. The response to stimulation within the lower visual field has a higher scalp distribution than that to upper field stimulation, suggesting that the response is generated in the visual cortex underlying the scalp electrodes. The response to patterns in the lateral hemifields (Fig. 1f and g) shows a contralateral distribution. It does not reveal the anomalous ipsilateral response that the evoked potential sometimes shows (e.g., 22) presumably because the paroxysmal response is more widespread and not confined to the calcarine fissure. Often the response is generalized, involving many brain areas other than the visual cortex, but even in these circumstances, the trigger may be cortical, because when the response is suppressed with sodium valproate (VPA), focal occipital activity can remain (23).

These findings are consistent with a seizure discharge triggered in the visual cortex, which sometimes remains within the visual cortex, and sometimes spreads to involve other areas.

Seizure onset involves one cerebral hemisphere or both hemispheres independently

This inference is based on several lines of evidence. In some patients, the response to stimulation in one lateral visual field (Fig. 1f or g) is far greater than that in the other field. In these patients, the response to diffuse intermittent light (when the stimulation is bilateral) shows a corresponding asymmetry, maximal over the hemisphere contralateral to the visual field giving the greater response. In these patients, the paroxysmal response appears to be triggered within one hemisphere and may remain confined within that hemisphere. Many patients show no such asymmetry, but even in these patients, it is possible to infer that the discharge occurs independently in the two hemispheres. First, as has already been mentioned, the response to a pattern presented in one hemifield has a contralateral scalp topography. Second, the response to the patterns in Fig. 1f and g, which stimulate only one cerebral hemisphere, is greater than that to the patterns in Fig. 1h and i, which stimulate both hemispheres. Although all the patterns have the same size, the response is greater when the activity is evoked within one hemisphere. This finding is consistent with other evidence that a critical amount of excitation within one hemisphere is necessary to evoke the discharge (see later). Third, the probability of a response to bilateral patterns such as in Fig. 1j is not markedly greater than that to unilateral patterns (Fig. 1f and g), even though the bilateral pattern is twice as large. As we will see in the

next section, doubling the size of a pattern usually greatly increases the probability of paroxysmal activity. This evidence for the independence of the two hemispheres in triggering a discharge is quite consistent with a trigger in the visual cortex and with the lack of callosal interconnections between the visual fields in posterior visual areas (V1, V2, V3, V3a, V4) (e.g., 24,25).

The triggering mechanism requires the physiologic activation of a critical area of cortical tissue

Any region of the visual cortex can evoke an epileptiform discharge, provided a sufficiently large area is stimulated. Symmetric patterns, as in Fig. 1k and l, have similar effects when their total area is equated. This is not the case with the patterns in Fig. 1m and n. If the pattern stimulates only the periphery (Fig. 1m), the probability of epileptiform discharge is reduced: a large annulus has the same effect as a small pattern that stimulates central vision (Fig. 1n). When the cortical projection of these patterns is equated, however, they also have similar effects, and the probability of a discharge is best predicted by the cortical magnification factor. The probability of a response to such patterns differs in each patient, but in such a way as to indicate that each patient's threshold can be expressed in terms of the area of cortex necessary to trigger a discharge (13).

Synchronization of the physiologic activation is necessary for epileptogenesis

As has already been mentioned, the vibration of a pattern to and fro in a direction orthogonal to the stripes greatly increases its epileptogenic potential. If, however, the movement is continuous in one direction rather than alternately reversing direction, the pattern ceases to be epileptogenic. This is the case when the contour velocities are equated, and when optokinetic nystagmus is avoided by using a bipartite pattern drifting toward central fixation (Fig. 1o) (26). The dramatic difference in the effects of drifting and vibrating (or phase-reversing) patterns is instructive in that it suggests an important role for the synchronization of large neuronal aggregates in the induction of a discharge. When the pattern alternately changes direction, the neurons sensitive to one direction of motion should fire, followed by a period during which cells sensitive to the opposite direction of motion should fire. The directional selectivity of neurons should ensure that the neuronal network exhibits a rhythmic and synchronized firing. The synchronized firing should not occur in response to a drifting grating because its contours will move into and out of the overlapping receptive fields, creating a sustained level of excitation. The very marked difference in the epileptogenic properties of drifting and vibrating patterns suggests that the synchronization that occurs with a vibrating or phase-reversing pattern is critical at the inception of the epileptic discharge, not simply a late reflection of the discharge itself.

The trigger involves the magnocellular pathways, but the resulting discharge may be more diffuse and involve both magnocellular and parvocellular divisions

The visual system is often conceived as divided into magno- and parvocellular divisions.

a. The magnocellular system does not generally code for color, which is of interest given that pattern-sensitive patients are not sensitive to gratings in which the stripes differ in color and not in brightness (27).
b. Neurons in the magnocellular system are directionally coded, and, as we have seen, pattern-sensitive patients are sensitive to moving patterns in a way that is clearly dependent on the direction of pattern motion (26).
c. Magnocellular neurons are tuned for binocular disparity. Patterns that fail to fuse in binocular vision are less epileptogenic than are those that fuse (27).
d. The magnocellular system has a lower spatial resolution than the parvocellular system. The patterns to which patients are sensitive tend to have a fairly low spatial frequency (27).
e. Magnocellular neurons have a higher temporal resolution than do parvocellular neurons. The upper frequency limit of sensitivity to diffuse intermittent photic stimulation can be >60 Hz (2).
f. The magnocellular system is thought to be part of the "dorsal stream," and in pattern-sensitive patients, the isolated spikes in response to a pattern tend to be most marked over parietal electrodes (23).

Wilkins (13) argued elsewhere that this evidence does not necessarily mean that the cortical hyperexcitability is confined to the magnocellular pathways, but simply that the discharge may start in the magnocellular division where the magnocellular projections offer the greatest opportunity for synchronizing cortical activity, given their high temporal resolution. If the hyperexcitability in Fixation-Off sensitivity (FOS) is largely confined to the parvocellular division, this conception would explain the seemingly paradoxic absence of photosensitivity in FOS.

Harding and Fylan (18) studied in patients with photosensitive epilepsy the response to phase-reversing patterns and found little saturation in the paroxysmal response at high contrasts relative to that shown by the occipital spike. These findings point to the participation of the parvocellular system (2).

ABNORMAL CONTRAST GAIN CONTROL IN VISUAL SENSITIVE EPILEPSY

The physiology of visual sensitivity also has been studied by using special parameters of the visual evoked potential (VEP) to investigate the cortical mechanisms

underlying the abnormal response to light, at levels below those at which paroxysmal activity is triggered (14,15). Patients with idiopathic photosensitive occipital lobe epilepsy (IPOLE) represent the ideal population in which this technique can be applied. In this syndrome, seizures are exclusively reflex and originate from the occipital lobe (28,29).

In the initial part of the study, transient flash and other pattern-reversal VEPs were tested. All patients showed significantly increased VEP amplitude, possibly reflecting hyperexcitability of the occipital cortex with increased neuronal synchronization (14). This phenomenon is similar to that hypothesized to underlie giant somatosensory evoked potentials seen in children with rolandic epilepsy (30), in which they correspond to the cortical spikes that are triggered by tapping of the extremities (30,31). Likewise, in patients with IPOLE, single flashes can produce time-locked occipital spikes (14). Averaging of these spikes entirely overlaps with the flash VEPs (14) (Fig. 2).

The second phase of the study by Porciatti et al. (15) analyzed responses to steady-state (S)-VEPs. Parameters of the visual stimuli were the same used in previous studies from Wilkins and co-workers, which are summarized in previous paragraphs. S-VEPs were recorded in response to simple visual patterns (black/white and red/green sinusoidal gratings with spatial frequency 2 cycles per degree and different contrast), sinusoidally contrast-reversed at various temporal frequencies.

VEPs to relatively low-frequency stimuli (4–10 Hz) with high contrast (90%) showed increased amplitude (Fig. 3), confirming the results previously obtained with transient VEPs. The subsequent step consisted in measuring the dependence of VEP amplitude and phase on stimulus contrast at two temporal frequency ranges, 4–10 Hz and 16–22 Hz (Fig. 4). Whereas the dependence on contrast at higher temporal frequency was comparable for patients and controls, a clear difference was found at the lower temporal frequency. The amplitude saturation at high contrasts and the phase advance with increasing contrast, typically found in normal subjects, were absent or much reduced in patients. The contrast threshold and the contrast dependence in the low-contrast range were not affected in patients. The critical range of reversal of square-wave patterns reported to elicit paroxysmal EEG activity (10–20 reversals per second) corresponds to a fundamental temporal frequency of 5–10 Hz, in agreement with the observed findings of sine-wave temporal modulation.

These results indicate that patterns with relatively low stimulus frequency and high contrast are effective in uncovering cortical hyperexcitability in visually sensitive patients, possibly because of an impairment of contrast gain-control mechanisms normally present at these temporal frequencies.

VEPs to high-contrast red/green equiluminant gratings tended to be larger than normal and showed a smaller phase advance in visually sensitive patients, although the

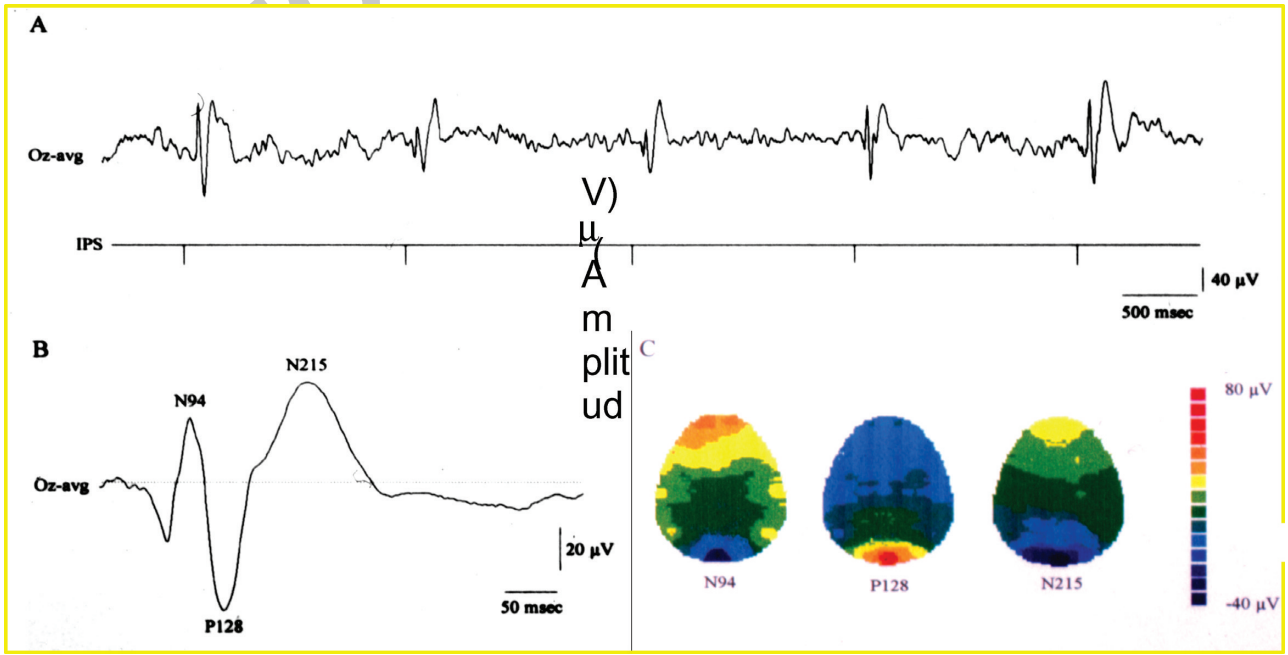

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FIG. 2. Patient with idiopathic photosensitive occipital lobe epilepsy (IPOLE), 15-year-old girl. **A:** Intermittent photic stimulation (IPS). At low-frequency stimulation, each flash produces an occipital spike. **B:** Flash(F)-visual evoked potential VEPs at Oz electrode are of very high amplitude. Oz, mid occipital electrode. **C:** F-VEP mapping. Latency from the beginning of the tracing is indicated below each map. Maps show occipital electric field distribution.

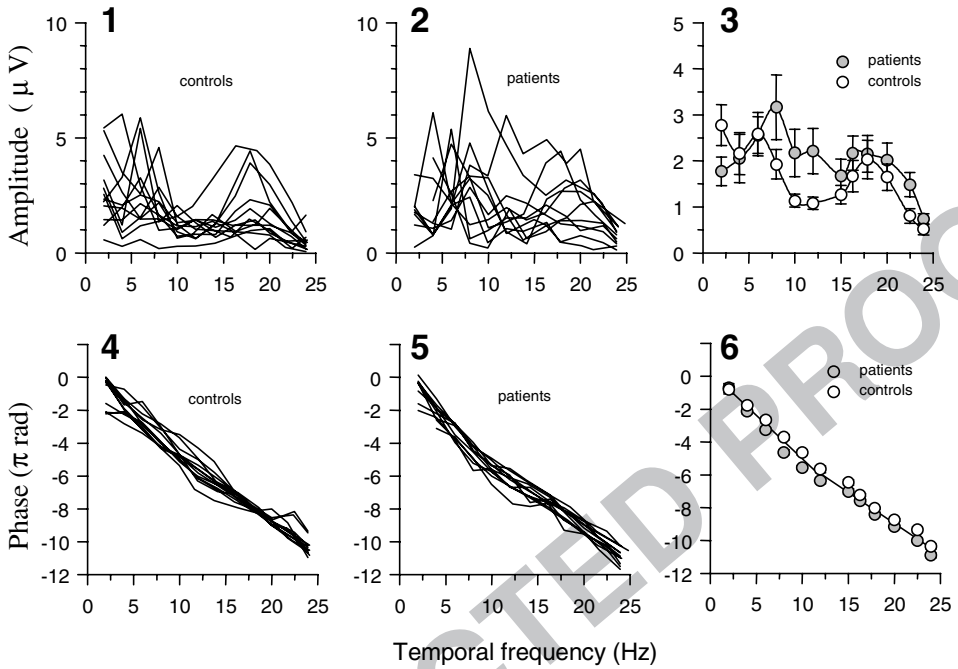

FIG. 3. Luminance-contrast gratings: effect of temporal frequency. Visual evoked potential (VEP) amplitude and phase plots of individual control subjects (1,4) and patients (2,5). (3,6) Average (SEM) VEP amplitude and phase of control subjects and patients are superimposed.

variation of amplitude with contrast did not significantly differ from those in normal subjects. These findings do not contradict the previous report that stationary equiluminant patterns are ineffective in inducing photoparoxysmal EEG activity (27).

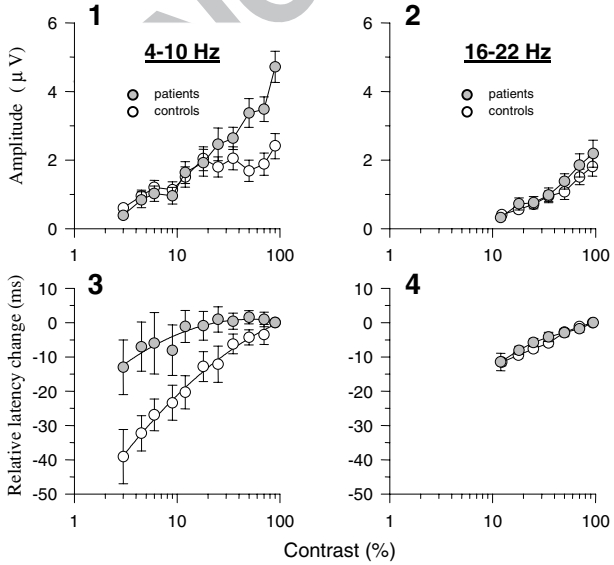

FIG. 4. Luminance-contrast gratings: effect of contrast. Average (SEM) amplitude (1,2) and latency (3,4) for two different ranges of temporal frequencies. In the 4- to 10-Hz range, the contrast dependence differed remarkably between controls and patients at medium-high contrast. In the 16- to 22-Hz range, the contrast dependence of amplitude (2) and phase (4) was virtually identical in control subjects and patients.

CONCLUSION

The study of the physiology of human visual sensitivity has attracted several groups of researchers, and they have approached this topic with different methods: (a) study of the physical characteristics of the trigger by using either complex visual stimuli, as they may appear in television commercials or videogames; (b) study of the typographic distribution and probability of the paroxysmal response to elementary visual stimuli that can be altered in their chromatic, temporal, and spatial parameters; and (c) use of VEPs to characterize mechanisms of control of cortical excitability below the critical levels that trigger paroxysmal activity.

These studies have allowed a series of inferences that represent the basis for further experiments: (a) triggering factors involve cells in the visual cortex; (b) ictal activity can be confined to the visual cortex or spread to other cortical regions, often following preferential pathways; and (c) an effective trigger requires activation of a critical mass of cortical neurons. The critical mass can be studied with area-summation experiments, taking into account the cortical magnification factor; (d) synchronization of the physiologic activation is necessary for epileptogenesis; (e) the magnocellular division may possibly have a greater involvement than the parvocellular; and (f) in visually sensitive individuals, cortical neurons in the occipital cortex show particular functional characteristics that may contribute to seizure precipitation (abnormal visual contrast gain control). Contrast gain control may be measured by using suitable VEP techniques.

FUTURE DIRECTIONS

VEPs in response to a wide variety of patterned visual stimuli can be used to define precisely the spatiotemporal window of cortical hyperexcitability under physiologic conditions: that is, the size and/or presentation time of visual stimuli sufficiently small to avoid paroxysmal activity. A better understanding of visually driven cortical dynamics is useful to (a) establish potentially dangerous regions of the visual spectrum, (b) design safer visual stimuli by eliminating hyperactivating visual stimuli, and (c) test the protective effects of drugs when subjects are exposed to hyperactivating stimuli.

REFERENCES

1. Quirk JA, Fish DR, Smith SJ, et al. First seizures associated with playing electronic screen games: a community-based study in Great Britain. *Ann Neurol* 1995;37:733–7.
2. Harding GFA, Jeavons PM. *Photosensitive epilepsy*. New ed. London: MacKeith Press, 1994.
3. Hayashi T, Ichiyama T, Nishikawa M, et al. Pocket Monsters, a popular television cartoon, attacks Japanese children. *Ann Neurol* 1998;44:427–8.
4. Ishida S, Yamashita Y, Matsuishi T, et al. Photosensitive seizures provoked while viewing "pocket monsters," a made-for-television animation program in Japan. *Epilepsia* 1998;39:1340–4.
5. Yamashita Y, Matsuishi T, Ishida S, et al. Pocket Monsters attacks Japanese children via media. *Ann Neurol* 1998;44:428. Q2
6. Harding GFA, Harding PF. Televised material and photosensitive epilepsy. *Epilepsia* 1999;40:65–9.
7. Kasteleijn-Nolst Trenite DG, Guerrini R, Binnie CD, et al. Visual sensitivity and epilepsy: a proposed terminology and classification for clinical and EEG phenomenology. *Epilepsia* 2001;42:692–701.
8. Takahashi Y, Fujiwara T, Yagi K, et al. Wavelength specificity of photoparoxysmal responses in idiopathic generalized epilepsy. *Epilesia* 1995;36:1084–8.
9. Badinand-Hubert N, Bureau M, Hirsch E, et al. Epilepsies and video games: results of a multicentric study. *Electroencephalogr Clin Neurophysiol* 1998;107:422–7.
10. Harding GFA. TV can be bad for your health. *Nat Med* 1998;4:265–7.
11. Takahashi Y, Fujiwara T, Yagi K, et al. Photosensitive epilepsies and pathophysiologic mechanisms of the photoparoxysmal response. *Neurology* 1999;53:926–32.
12. Takahashi Y, Sato T, Goto K, et al. Optical filters inhibiting television-induced photosensitive seizures. *Neurology* 2001; 57:1767–73.
13. Wilkins AJ. Towards an understanding of reflex epilepsy and the absence. In: Duncan JS, Panayiotopoulos CP, eds. *Typical absences and related epileptic syndromes*. London: Churchill, 1995:196–205.
14. Guerrini R, Bonanni P, Parmeggiani L, et al. Induction of partial seizures by visual stimulation: clinical and electroencephalographic features and evoked potentials studies. *Adv Neurol* 1998;75:159–78.
15. Porciatti V, Bonanni P, Fiorentini A, et al. Lack of cortical contrast gain control in human photosensitive epilepsy. *Nat Neurosci* 2000;3:259–63.
16. Fylan F, Harding GFA. The effect of television frame rate on EEG abnormalities in photosensitive and pattern-sensitive epilepsy. *Epilepsia* 1997;38:1124–31.
17. Ricci S, Vigevano F, Manfredi M, et al. Epilepsy provoked by television and video games: safety of 100-Hz screens. *Neurology* 1998;50:790–3.
18. Harding GFA, Fylan F. Two visual mechanisms of photosensitivity. *Epilepsia* 1999;40:1446–51.
19. Tobimatsu S, Zhang YM, Tomoda Y, et al. Chromatic sensitive epilepsy: a variant of photosensitive epilepsy. *Ann Neurol* 1999;45:790–3.
20. Binnie CD, Estevez O, Kasteleijn-Nolst Trenité DGA, et al. Colour and photosensitive epilepsy. *Electroencephalogr Clin Neurophysiol* 1984;58:387–91.
21. Independent Television Commission guidance note for licensees on flashing images and regular patterns in televisione. Available from URL: http://www.itc.org.uk/itc_publications/codes_guidance/flashing_images/index.asp
22. Blumenhardt LD, Halliday AM. Hemisphere contributions to the composition of the pattern-evoked potential waveform. *Exp Brain Res* 1979;36:53–69.
23. Darby CE, Park DM, Wilkins AJ. EEG characteristics of epileptic pattern sensitivity and their relation to the nature of pattern stimulation and the effects of sodium valproate. *Electroencephalogr Clin Neurophysiol* 1986;63:517–25.
24. Zeki S, Shipp S. The functional logic of cortical connections. *Nature* 1988;335:311–7. Review.
25. Ffytche DH, Howseman A, Edwards R, et al. Human area V5 and motion in the ipsilateral visual field. *Eur J Neurosci* 2000;12:3015–25.
26. Binnie CD, Findlay J, Wilkins AJ. Mechanisms of epileptogenesis in photosensitive epilepsy implied by the effects of moving patterns. *Electroencephalogr Clin Neurophysiol* 1985;61:1–6.
27. Wilkins AJ, Darby CE, Binnie CD. Neurophysiological aspects of pattern-sensitive epilepsy. *Brain* 1979;102:1–25.
28. Guerrini R, Dravet C, Genton P, et al. Idiopathic photosensitive occipital lobe epilepsy. *Epilepsia* 1995;36:883–91.
29. Guerrini R, Bonanni P, Parmeggiani L, et al. Adolescent onset of idiopathic photosensitive occipital epilepsy after remission of benign rolandic epilepsy. *Epilepsia* 1997;38:777–81.
30. Tassinari CA, De Marco P, Plasmati R, et al. Extreme somatosensory evoked potentials (ESEPs) elicited by tapping of hands or feet in children: a somatosensory cerebral evoked potentials study. *Neurophysiol Clin* 1988;18:123–8.
31. De Marco P, Tassinari CA. Extreme somatosensory evoked potentials (ESEP): an EEG sign forecasting the possible occurrence of seizures in children. *Epilepsia* 1981;22:569–75.

Queries

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